

**Remarks**

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claim 94 has been amended to recite a “<sup>15</sup>N/<sup>13</sup>C-labeled protein sample.” Support for this amendment is found, for example, at paragraph [0172] of the specification. Claims 1-133 are pending, with claims 1-93 being withdrawn. No excess claims fees are due with this submission.

The rejection of claims 94-133 for nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40 of U.S. Patent No. 7,141,432 to Szyperski (“Szyperski”) is respectfully traversed.

It is the position of the U.S. Patent and Trademark Office (“PTO”) that the conflicting claims are not patentably distinct from each other because the claims differ only in the following in the following terminology: the instant application recites “protein sample” instead of “<sup>15</sup>N/<sup>13</sup>C-labeled protein sample” as recited in claims 1-40 of Szyperski and the instant application recites detecting chemical shift values in a “phase sensitive manner.”

Claims 1-40 of Szyperski are drawn to a method for obtaining rapid and complete assignments of chemical shift values of <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N of a protein molecule comprising: providing a <sup>15</sup>N/<sup>13</sup>C-labeled protein sample; and conducting four RD NMR experiments on the protein sample, where (1) a first experiment is selected from the group consisting of a RD 3D  $\underline{H}^{\alpha/\beta} \underline{C}^{\alpha/\beta}$  (CO)NHN NMR experiment, a RD 3D  $\underline{HA}, \underline{CA}, (CO), N, HN$  NMR experiment, and a RD 3D  $\underline{H}, \underline{C}, (C-TOCSY-CO), N, HN$  NMR experiment for obtaining sequential correlations of chemical shift values; (2) a second experiment is selected from the group consisting of a RD 3D HNN $\underline{CAHA}$  NMR experiment, a RD 3D  $\underline{H}^{\alpha/\beta}, \underline{C}^{\alpha/\beta}, N, HN$  NMR experiment, and a RD 3D HNN< $\underline{CO}, \underline{CA}$ > NMR experiment for obtaining intraresidue correlations of chemical shift values; (3) a third experiment is a RD 3D  $\underline{H}, \underline{C}, C, H-COSY$  NMR experiment for obtaining assignments of sidechain chemical shift values; and (4) a fourth experiment is a RD two-dimensional (2D)  $\underline{HB}, \underline{CB}, (CG, CD), HD$  NMR experiment for obtaining assignments of aromatic sidechain chemical shift values.

Thus, claims 1-40 of Szyperski are not directed to “[a] method for obtaining assignments of chemical shift values of <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N of a protein molecule comprising: providing a <sup>15</sup>N/<sup>13</sup>C-labeled protein sample; and conducting four reduced dimensionality (RD) nuclear magnetic resonance (NMR) experiments on the protein sample, wherein the

chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum are detected in a phase sensitive manner and (1) a first experiment is selected from ... (emphasis added)” as set forth in claims 94-133 of the present application.

In order to make a rejection for nonstatutory obviousness-type double patenting, the Manual of Patent Examining Procedure (“MPEP”) states that the PTO must show that the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). MPEP § 804 (II)(B)(1) (2006) See, *e.g.*, *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed Cir. 1993); and *In re Longi*, 759 F. 2d 887, 225USPQ 645 (Fed. Cir. 1985). At MPEP § 804 (II)(B)(1) it states that “[i]n determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is – does any claim in the application define an invention that is anticipated by, or is merely an obvious variation of, an invention claimed in the patent?” In this case, the applicants assert that the answer is “no.” Moreover, “obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the subject matter claimed in a commonly owned patent . . . when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent.” MPEP § 804(II)(B)(1) (2006) (citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 USQP2d 1869 (Fed. Cir. 2001); *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000) (emphasis in original)). “When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art.” MPEP § 804(II)(B)(1) (2006) (citing *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992).

The PTO has failed to meet its burden. In particular, in support of its rejection for nonstatutory obviousness-type double patenting, the PTO asserts that the expression “phase-sensitive manner” in the claims of the present application is one of the embodiments of the method recited in Szyperski and its obvious variation. Applicants respectfully disagree.

In particular, as set forth in the attached Declaration of Thomas A. Szyperski Under 37 C.F.R. § 1.132 (“Szyperski Declaration”) the claims of Szyperski neither disclose

nor suggest detection of chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum in a phase sensitive manner, as required by the claims of the present application (emphasis added). More specifically, in Szyperski, chemical shifts (also referred to as the ‘projected chemical shifts’) inferred in RD NMR experiments from the frequency difference of two peaks forming a peak pair arise from cosine modulation (*see, e.g.*, Szyperski at column 4, lines 12-24, column 4, lines 44-55, col. 5, lines 8-22, col. 5, lines 44-57, col. 6, lines 7-18, col. 6, lines 36-47, col. 6, line 65 to col. 7, line 8, and col. 7, lines 23-33) (Szyperski Declaration ¶ 8). Chemical shifts which are detected using cosine modulation are *not* measured in a phase-sensitive manner (Szyperski Declaration ¶ 8). That is, in Szyperski, the frequency difference can relate to a chemical shift being either downfield or up-field to the carrier frequency of the radio-frequency pulse exciting the corresponding spins (Szyperski Declaration ¶ 8). In RD NMR, as described in Szyperski, this ambiguity must be resolved by placing the carrier at the edge of the spectral range so that *all* frequency differences correspond to chemical shifts being either downfield or up-field from the carrier frequency (Szyperski Declaration ¶ 8). This, however, requires that the spectral width and thus the number of increments that are required to reach a given maximal evolution time has to be increased. In turn, the minimal measurement time is increased by the same amount (Szyperski Declaration ¶ 8).

Szyperski does teach the generation of certain NMR signals encoding the chemical shift values of  $^{13}\text{C}_{i-1}^{\alpha}$  and  $^{15}\text{N}_i$  (col. 4, lines 8-9),  $^{13}\text{C}_{i-1}^{\text{ali}}$  and  $^{15}\text{N}_i$  (col. 4, lines 40-42),  $^{13}\text{C}_i^{\alpha}$ ,  $^{13}\text{C}_i^{\beta}$ , and  $^{13}\text{C}_i^{\gamma}$  (col. 5, lines 4-5),  $^{13}\text{C}_i^{\alpha}$ ,  $^{13}\text{C}_i^{\beta}$ , and  $^{15}\text{N}_i$  (col. 5, lines 39-41),  $^{13}\text{C}^m$  and  $^{13}\text{C}^n$  (col. 6, lines 3-5 and 32-33),  $^{13}\text{C}^{\beta}$  (col. 6, lines 61-63), and  $^{13}\text{C}^m$  (col. 7, lines 20-21) in a phase sensitive manner (Szyperski Declaration ¶ 9). However, this does not relate to detection of chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum in a phase sensitive manner, as required by the claims of the present invention (emphasis added) (Szyperski Declaration ¶ 9). In contrast, all teachings in Szyperski relating to chemical shifts of  $^{13}\text{C}$  and  $^1\text{H}$  inferred in RD NMR experiments from the frequency difference of two peaks forming a peak pair arise from cosine modulation (Szyperski Declaration ¶ 9). As described above, chemical shifts arising from cosine modulation are not measured in a phase sensitive manner (Szyperski Declaration ¶ 9). Szyperski neither attempts to nor achieves the determination of chemical shift values of  $^1\text{H}$  and  $^{13}\text{C}$  which are encoded in peak pairs of an NMR spectrum in a phase sensitive manner (Szyperski Declaration ¶ 9).

This key drawback of RD NMR as disclosed in Szyperski is resolved by introducing the sine modulation as described in the present patent application (Szyperski Declaration ¶ 10). The sine modulation results in an anti-phase peak pair in which either the up-field or the down-field peak is of positive sign (while the other peak of the peak pair is of negative sign) (Szyperski Declaration ¶ 10). Hence, the distinction of a peak pair with ‘positive peak up-field and negative peak down-field’ from a peak pair with ‘negative peak up-field and positive peak down-field’ enables phase sensitive detection of the chemical shift inferred from the separation of the peaks of the peak pairs generated by sine modulation (Szyperski Declaration ¶ 10). The experiments disclosed in the present application represent the fastest possible way to phase-sensitively detect projected chemical shifts encoded in a frequency separation of two peaks (Szyperski Declaration ¶ 10). In spite of the fact that cosine-modulation based RD NMR was first published in 1993 (Szyperski et al., “Reduced Dimensionality in Triple Resonance Experiments,” *J. Am. Chem. Soc.* 115:9307-9308 (1993)), the value of sine modulation of signals for phase-sensitive detection of projected chemical shifts has neither been recognized nor considered for designing new experiments. This fact demonstrates the non-obviousness of the present invention.

The rejection of claims 94-133 under 35 U.S.C. § 112, first paragraph, for lack of enablement is obviated in view of the above amendments incorporating the term “ $^{15}\text{N}/^{13}\text{C}$ -labeled protein sample.” Thus, this rejection of claims 94-133 should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: December 12, 2007

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